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Re-evaluation Note REV2015-09

Special Review of Fluazifop-P-butyl: Proposed Decision for Consultation

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1.0 Introduction

Pursuant to subsection 17(2) of the *Pest Control Products Act*, the PMRA has initiated a special review of pest control products containing fluazifop-P-butyl as a result of the Norwegian decision to prohibit all uses of this active ingredient in Norway due to human health concerns (Rotterdam Convention, 2001). The initiation of the special review was announced in Re-evaluation Note REV2013-06, *Special Review Initiation of 23 Active Ingredients*.

Pursuant to subsection 18(4) of the *Pest Control Products Act*, the PMRA has evaluated the aspects(s) of concern that prompted the special review of pest control products containing fluazifop-P-butyl. The aspect of concern is relevant to human health and was identified as the potential for developmental and reproductive effects of fluazifop-P-butyl.

2.0 Uses of Fluazifop-P-butyl in Canada

Fluazifop-P-butyl was first registered in Canada in 1989. Fluazifop-P-butyl is a post-emergent herbicide that is used to control grass weeds in broadleaf crops and ornamentals. It acts by inhibiting fatty acid synthesis in the plant. Fluazifop-P-butyl is applied 1-3 times per year with an application rate of up to 250 g a.i./ha. The commercial end-use product is formulated as an emulsified concentrate and is applied using ground spray equipment or handheld equipment.

In Canada, fluazifop-P-butyl underwent re-evaluation in 2011. The re-evaluation included an assessment of the risks to human health and environment from all uses of fluazifop-P-butyl (Canada, 2011, Canada, 2012).

Currently, there is one technical grade active ingredient and one commercial class product registered in Canada under the authority of the *Pest Control Products Act* (Appendix I) and both products are considered in this review. The proposed special review decision is applicable for all registered products containing fluazifop-P-butyl.

3.0 Aspect of the Pest Control Product that Prompted the Special Review

The use of fluazifop-P-butyl as a pesticide in Norway was banned due to human health concerns related to potential developmental and reproductive effects. The expected effect of the regulatory action was identified in the Rotterdam Convention PIC Circular XIII (Rotterdam Convention, 2001) and the Form for Notification of Final Regulatory Action to Ban or Severely Restrict a Chemical (Norway) as "*complete risk reduction*". The reasons for the Norwegian regulatory action, as outlined in the PIC Circular, were relevant to human health and were summarised as follows:

"*Fluazifop-P-butyl has shown in animal studies, rat and rabbit, that it causes effects on reproduction and that it is a teratogen. This means that it also has the potential to cause these effects in humans. The risk of this happening is higher for the workers than for the consumers, although it is also possible that residues can be high and thus also be a risk to the consumer too.*" (Rotterdam Convention, 2001)

Based on the review of the Norwegian information, the PMRA has defined the aspect of concern that prompted the special review of pest control products containing fluazifop-P-butyl as the potential for developmental and reproductive effects of fluazifop-P-butyl.

4.0 PMRA Evaluation of the Aspect of the Pest Control Product that Prompted the Special Review

Following the initiation of the special review of pest control products containing fluazifop-P-butyl, the PMRA requested information from provinces and other relevant federal departments and agencies, in accordance with subsection 18(2) of the *Pest Control Products Act*. No information relevant to the aspect of concern was received,

In order to evaluate fluazifop-P-butyl's potential developmental and reproductive effects, the PMRA has considered currently available relevant scientific information, which includes information considered for the re-evaluation of fluazifop-P-butyl and any relevant information obtained since the re-evaluation (for example, reproduction and developmental studies, and information from the Canadian incident report database).

The PMRA considered several developmental toxicity studies (in rats and rabbits) and a two-generation reproduction study in rats as a part of the human health assessment (Canada, 2011, United States, 2005, United States, 2008, United States, 2014). Fluazifop-P-butyl has an overall developmental NOAEL of 2.0 mg/bw kg/day which was selected based on decreased fetal weights, increased incidence of hydroureter and delayed ossifications. An overall maternal NOAEL of 100 mg/kg bw/day was concluded based on maternal weight decrease in the Wistar rat studies. In the available rat developmental studies, increased susceptibility of offspring was observed relative to maternal animals; however, the degree of concern for the observed effects is low as they are not classified to be serious effects or malformations.

Based on the information from reproductive studies, the parental NOAELs of 0.74 mg/kg bw/day and 7.1 mg/kg bw/day were established for males and females, respectively. The offspring NOAEL was 7.1 mg/kg bw/day based on decreased viability of F1 and F2 pups during lactation. A NOAEL of 0.74 mg/kg bw/day was determined for reproductive toxicity in males and a NOAEL of 0.88 mg/kg bw/day for reproductive toxicity in females.

The European Food Safety Authority selected the same developmental and reproductive endpoints (EFSA, 2012).

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects unless it is determined on the basis of reliable scientific data that a different margin of safety would be appropriate. This factor takes into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, as well as potential pre- and post-natal toxicity. With respect to the completeness of the toxicity database, the fluazifop-P-butyl database contains the full complement of required studies, including developmental studies in rats and rabbits, and a two-generation reproductive study in rats.

There is evidence of pre/post-natal toxicity resulting from exposure fluazifop-P-butyl. There are indications of increased susceptibility in rat fetuses in the absence of maternal toxicity. However, these effects are considered to be a developmental delay as opposed to malformations. Overall, the degree of concern for increased sensitivity in young is low and there is no residual uncertainty for pre and/or post-natal toxicity.

Based on the available toxicology information, there were no concerns for neurotoxicity resulting from exposure to fluazifop-P-butyl at relevant exposure levels. There was no evidence of clinical signs indicative of neurotoxicity or neuropathology in the available studies.

In consideration of the above, the *Pest Control Products Act* factor was reduced to 1-fold.

5.0 Human Health Exposure and Risk Assessment

In addition to characterizing the developmental and reproductive toxicity of fluazifop-P-butyl, the PMRA has conducted a scientifically-based risk assessment to determine if exposure to fluazifop-P-butyl presents an unacceptable risk to Canadians. Toxicology endpoints selected for risk assessment are considered protective of any potential developmental or reproductive effects.

As part of the assessment, the PMRA estimated the short-term and intermediate-term risk to workers mixing/loading and applying pest control products containing fluazifop-P-butyl. For short-term occupational dermal and inhalation exposure, a NOAEL of 2.0 mg/kg bw/day was selected based on a developmental toxicity study in rats. For intermediate-term occupational dermal and inhalation exposure, a NOAEL of 0.74 mg/kg bw/day was selected based on the 2-generation reproductive toxicity study in rats. Short-, intermediate-term combined (dermal plus inhalation) exposure for workers mixing/loading and applying products containing fluazifop-P-butyl using groundboom, manually-pressurized handgun and backpack sprayers is not expected to be of concern based on the personal protective equipment (PPE) currently included on the label.[1]

In addition, postapplication exposure is not of concern for workers conducting scouting, irrigation and hand weeding activities on the day of application and hand-harvesting on the day of the pre-harvest-interval.

There are no residential uses of fluazifop-P-butyl registered in Canada. Therefore, aggregate exposure is limited to food and drinking water.

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[1] To minimize the potential exposure to workers, the current label includes the PPE such as "Coveralls over long-sleeved shirt and long pants, chemical resistant gloves, socks and chemical resistant footwear during mixing, loading, application, clean-up and repair. Wear goggles or face shield during mixing/loading."

For acute dietary exposure, an acute reference dose (ARfD) of 0.5 mg/kg bw for females age 13-49 was selected based on a NOAEL of 50 mg/kg bw/day from a developmental toxicity study in rats.[2] An acute reference dose (ARfD) was not established for the general population as there was no appropriate endpoint attributable to a single dose identified in the available studies including the developmental toxicity studies. Acute dietary exposure (food and drinking water), for domestic and imported food commodities is not of concern for females age 13-49 (<7% of the ARfD at 95th percentile). Acute aggregate exposure is limited to food and drinking water and is also not of concern.

For chronic dietary exposure, an acceptable daily intake (ADI) of 0.005 mg/kg bw/day was selected based on a NOAEL of 0.5 mg/kg bw/day from a 90 day rat feeding study. No cancer endpoint was established for fluazifop-P-butyl. Chronic dietary exposure (food and drinking water) for domestic and imported food commodities is not of concern for all population subgroups (<61% of the ADI). The highest exposed population subgroup is infants less than 1 year of age. Chronic aggregate exposure is limited to food and drinking water and is also not of concern.

A common mechanism of toxicity has not been identified for fluazifop-P-butyl and other active ingredients. Therefore, a cumulative risk assessment is not required for fluazifop-P-butyl.

No concerns related to the aspect of concern (potential developmental and reproductive effects of fluazifop-P-butyl) were identified in the information received through the Canadian incident report database.

The PMRA follows a risk-based scientific approach in determining the risk to human health from pesticides. This approach takes into consideration both the estimated level of exposure and the toxicity of the pesticide. Based on the above assessment, the PMRA concludes that there are no developmental or reproductive risks of concern to occupational workers, or from consumption of food and drinking water, when pest control products containing fluazifop-P-butyl are applied according to the current conditions of use. No additional risk mitigation measures are required.

6.0 Proposed Special Review Decision for Fluazifop-P-butyl

Evaluation of available scientific information related to the aspect of concern (the potential developmental and reproductive effects of fluazifop-P-butyl) indicated that the use of pest control products containing fluazifop-P-butyl do not pose unacceptable risks to human health, taking into account current conditions of use. On this basis, Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Product Act*, is proposing to confirm the current registration of fluazifop-P-butyl products for sale and use in Canada. This proposal affects all registered products containing fluazifop-P-butyl (technical and end-use products) registered in Canada.

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[2] Based on diaphragmatic hernia malformations which may occur after a single dose

This proposed special review decision is a consultation document.[3] The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to Publications (please see contact information on the cover page of this document).

7.0 Next Steps

Before making a special review decision on fluazifop-P-butyl, the PMRA will consider all comments received from the public in response to this consultation document. A science based approach will be applied in making a final decision on fluazifop-P-butyl. The PMRA will then publish a special review decision document, which will include the decision, the reasons for it, a summary of the comments received on the proposed decision and the PMRA's response to these comments.

[3] "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

Appendix I

Table 1 Registered Products Containing Fluazifop-P-butyl as of 21 April 2015

Registration Number	Marketing Class	Registrant	Product Name
21208	Technical	Syngenta Canada Inc.	FLUAZIFOP-P-BUTYL TECHNICAL
21209	Commercial	Syngenta Canada Inc	VENTURE L HERBICIDE

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Published Information

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2530508 United States. 2005. Environmental Protection Agency. Fluazifop-P-butyl: Revised HED Chapter of the Tolerance Reassessment Eligibility Document (TRED)

2530504 United States. 2008. Environmental Protection Agency. Fluazifop-P-butyl. Amended Human Health Risk Assessment to Support Use on Dry Beans, Peanuts and Post-bloom Application to Soybeans.

2530507 United States. 2014. Environmental Protection Agency. Fluazifop-P-butyl. Human Health Risk Assessment Scoping Document in Support of Registration Review

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Unpublished Information

2530506 Norway. Form For Notification of Final Regulatory Action to Ban or Severely Restrict a Chemical *Fluazifop-P-butyl*. Norwegian Agricultural Inspection Service